Clinico-pathological Conference

Recurrent pseudomembranous colitis due to *Clostridium difficile* in AIDS

D R Churchill, S B Lucas, I Williams, N M Foley, R F Miller

Department of Medicine, Middlesex Hospital, London, W1N 8AA
D R Churchill

Department of Histopathology
S B Lucas

Academic Department of Genitourinary Medicine
I Williams

Department of Medicine, University College London Medical School, London, W1N 8AA
R F Miller

Department of Thoracic Medicine, Royal Free Hospital, London NW3 2QG
N M Foley

Address correspondence to: Dr R F Miller, Department of Medicine, UCLMS, First Floor Crosspiece, Middlesex Hospital, London, W1N 8AA, UK

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Case report (Dr D R Churchill)

A 34 year old homosexual Afro-Caribbean man was admitted with a one week history of profuse watery diarrhoea, passing liquid stools every 15–20 minutes, and diffuse abdominal pain. Eleven days previously he had completed a 7 day course of oral flucloxacillin (500 mg four times daily) and intravenous cefuroxime (750 mg three times daily) as treatment for cellulitis of his forearm and a bacterial chest infection.

The patient had been born in the West Indies but had lived in England since he was two years old. Four years before this admission he was found to be HIV-1 antibody positive and two years later he had bronchoscopically confirmed *Pneumocystis carinii* pneumonia, at which time cutaneous and palatal Kaposi's sarcoma was noted. He had a second episode of pneumocystis pneumonia four months before the onset of his current symptoms; following this episode he had begun secondary antipneumocystis prophylaxis with monthly inhaled pentamidine.

Examination on admission showed him to be pyrexial, 38°C, clinically dehydrated, hypotensive (BP = 95/75 mmHg) lying down and oliguric. Investigations showed serum creatinine was 242 (normal = 50–125) μmol/l, blood urea = 21·7 (normal = 3·0–8·0) mmol/l. The total white blood cell count was $1·8 \times 10^9$/l (neutrophils $0·8 \times 10^9$/l) and the CD4 count was 0·01 (normal = 0·35–2·2) $\times 10^9$/l being 1% of the total lymphocyte count. He was given intravenous rehydration and his clinical condition and renal function tests improved. However his diarrhoea persisted. Stool culture was negative for *Shigella*, *Salmonella* and *Campylobacter* species, and acid and alcohol fast bacilli (AAFB) were not seen. Two days after admission he developed abdominal distension and rebound tenderness. An abdominal radiograph showed marked gaseous distension of the transverse colon (fig 1). Sigmoidoscopy revealed liquid bloody stool and a mild proctitis. The following day *Clostridium difficile* toxin was found in the stools. Oral vancomycin (125 mg four times daily) was given for seven days; his diarrhoea and abdominal pain rapidly improved. The day after completing vancomycin he again became unwell with fever, dyspnoea and a non-productive cough. Arterial blood gases revealed hypoxia, PaO_2 = 8·0kPa, breathing air, and a chest radiograph showed consolidation in the left mid zone; blood cultures were negative. It was felt he had a bacterial pneumonia and he was treated initially with oral erythromycin and when he failed to respond to this, treatment was changed to intravenous cefuroxime (750 mg three times daily), flucloxacillin (400 mg four times daily) and gentamicin (80 mg three times daily). The patient made a slow but steady recovery.

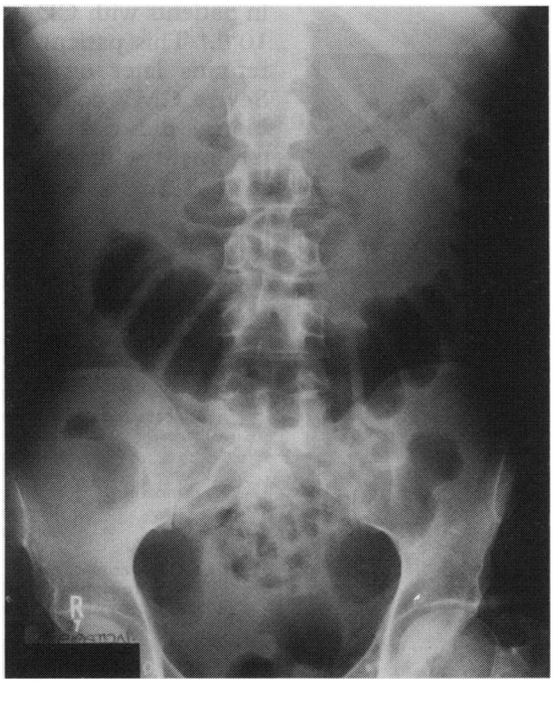

Figure 1 Plain abdominal radiograph showing marked gaseous distension of the transverse colon.

Twenty three days after admission he suddenly became unwell with a high fever of 39·5°C. At this time he was neutropenic, $0·6 \times 10^9$/l. A repeat sample of stool was negative for *C difficile* toxin but *Staphylococcus epidermidis* was isolated from blood cultures. Intravenous teicoplanin (200 mg once daily) was given for 8 days and the patient rapidly recovered, only to develop left orchitis due to *Pseudomonas aeruginosa*. This was complicated by an epididymal abscess which required surgical drainage and a further course of gentamicin was given.

After 7 weeks in hospital the patient was discharged to a hospice. He remained there for four weeks but was then readmitted with a two week history of constant lower abdominal pain and rectal bleeding without diarrhoea.

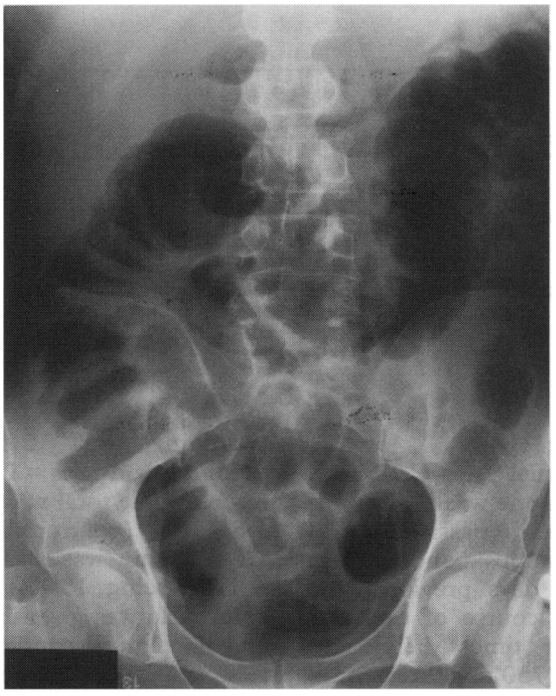

Figure 2 Plain abdominal radiograph showing extensive "thumb printing" of colonic mucosa, in addition to gaseous distension.

An abdominal radiograph (fig 2) showed gaseous distension of the colon with extensive "thumb printing" of the colonic mucosa. Sigmoidoscopy revealed florid pseudomembranous colitis. Rectal biopsy confirmed a proctitis: no crypt abscesses were seen and special stains did not detect cryptosporidia or cytomegalovirus. A stool sample was positive for *C difficile* toxin. A further course of oral vancomycin was prescribed with rapid improvement in symptoms. Subsequent stool samples on day 16 and day 21 were negative for *C difficile* toxin. Two weeks later diarrhoea recurred and *C difficile* toxin was identified in the stool; oral metronidazole (400 mg three times daily) was given with resolution of symptoms and the stool was again negative for *C difficile* toxin.

This time the patient reported visual disturbance in both eyes, cytomegalovirus retinitis was diagnosed on the basis of typical retinal appearances. Ganciclovir was commenced (5 mg/kg intravenously twice daily) and a Hickman line was inserted. After three weeks treatment there had been stabilisation in visual symptoms and an improvement in retinal appearances and so ganciclovir was reduced to maintenance dose (5 mg/kg intravenously daily). A chest radiograph taken after placement of the Hickman line (fig 3) showed diffuse shadowing. In the lower zones the shadowing was patchy but more confluent in the upper zones. Fibreoptic bronchoscopy was performed and showed extensive endobronchial Kaposi's sarcoma. Bronchoalveolar lavage from the right lower lobe was negative for *P carinii* and other pathogens.

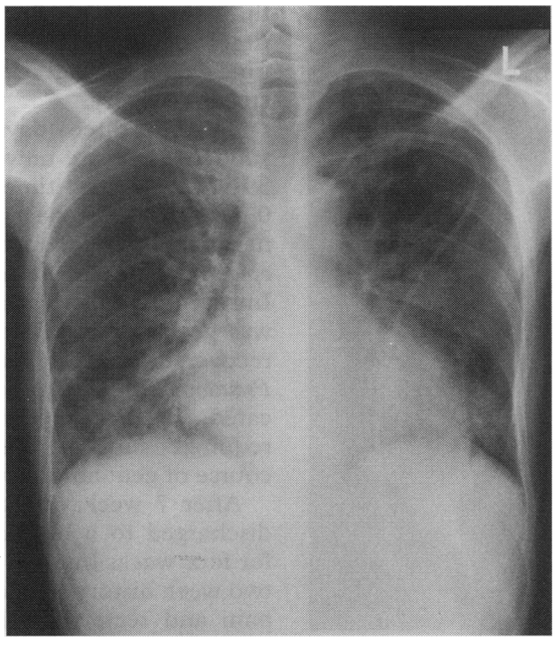

Figure 3 Chest radiograph showing Hickman line and bilateral diffuse shadowing.

It was planned to give chemotherapy as treatment for the pulmonary Kaposi's sarcoma but the patient's condition suddenly deteriorated with onset of diffuse abdominal pain and profuse diarrhoea. Stool cultures were again positive for *C difficile* toxin. Terminally the patient became hypotensive and clinically septicaemic; despite resuscitative measures he died eleven weeks after admission.

Discussion (Dr. I Williams)

This 34 year old man had advanced HIV disease with profound immunosuppression. His CD4 count was $0{\cdot}01 \times 10^9$/l and he had pneumocystis pneumonia two years previously. He then presented with severe diarrhoea, abdominal pain, salt and water depletion and fever. There are several possible causes for acute diarrhoea in this population of patients.[1] (table 1) Firstly, cryptosporidiosis may present with profuse watery diarrhoea and abdominal pain.[2,3] In advanced HIV disease it is difficult to treat and is associated with a poor prognosis. In this patient examination of multiple stool specimens and rectal biopsy did not demonstrate cryptosporidium. Secondly, cytomegalovirus (CMV) disease is common in patients with CD4 counts less than $0{\cdot}05 \times 10^9$/l.[4] This patient was noted to have CMV retinitis later on the course of his illness. Severe CMV colitis[5] can occur but the rectal biopsy did not show typical features, and treatment with ganciclovir did not influence

Table 1 Causes of diarrhoea in HIV-infected patients

(A) Infections		
	(i) bacteria	*Salmonella* species
		Shigella species
		Clostridium difficile
		Campylobacter jejuni
	(ii) mycobacteria	*Mycobacterium avium-intracellulare*
	(iii) viruses	cytomegalovirus
		Herpes simplex virus
		adenovirus
	(iv) protozoa	*Cryptosporidium*
		Microsporidia
		Isospora belli
(B) Other causes		
	(i) HIV enteropathy	
	(ii) extensive Kaposi's sarcoma	
	(iii) lymphoma of small bowel	
	(iv) chronic pancreatitis	
	(a) secondary to HIV infection	
	(b) secondary to therapy	

the diarrhoeal illness; however, it remains a possibility in this patient. The abdominal tenderness and marked distension of the transverse colon seen on the abdominal radiograph suggest a toxic megacolon. Bacterial enteric infections are known to cause severe colitis in patients with HIV disease particularly *Shigella* and *Salmonella* species.[2 6] Repeated stool cultures for bacteria were negative in this man. Of other non-infectious causes of diarrhoea, Kaposi's sarcoma in the gut can cause symptoms if extensive but lesions are often clinically silent.[2 7] This patient had both cutaneous and palatal Kaposi's sarcoma diagnosed two years previously but it is unlikely that bowel involvement was contributing to his illness. The incidence of non-Hodgkin's lymphoma is increased in patients with advanced HIV disease and in the bowel may present with multiple symptoms, depending on the site, including abdominal pain and diarrhoea.

The clinical presentation in this man suggests an acute gastrointestinal infection and the subsequent finding of *Clostridium difficile* toxin in stool cultures and the presence of pseudomembranes on sigmoidoscopy confirmed this. In case series of infectious causes of diarrhoea in patients with AIDS, *Clostridium difficile* has been reported, but it appears to be an uncommon pathogen.[8 9] In view of the marked immunosuppression, high rate of hospitalisation and frequent use of antibiotics in patients with AIDS this seems surprising and may represent under diagnosis. Numerous antibiotics have been implicated in causing pseudomembranous colitis. This patient received treatment for a cellulitis prior to his admission with diarrhoea, subsequently he was given several courses of antibiotics for a bacterial pneumonia and an epididymal abscess. Antibiotic-associated diarrhoea may occur in the absence of *Clostridium difficile* but when *Clostridium difficile* is present it is associated with pseudomembranous colitis and may cause severe abdominal pain, fever, bloody diarrhoea, toxic megacolon and secondary bowel perforation.[8] Despite treatment with both vancomycin and metronidazole, this patient's recurrent episodes of *Clostridium difficile* infection were probably secondary to persistent carriage of the organism in the gut, rather than due to re-infection. Use of alternative treatment, such as cholestyramine, would not have altered the outcome. Multiple factors such as an underlying HIV enteropathy, the presence of CMV, recurrent bacterial infections and the profound immuno-suppression may have all contributed to this patient's diarrhoeal disease and outcome.

The finding of endobronchial Kaposi's sarcoma at bronchoscopy may have made this patient more susceptible to bacterial pneumonia, alternatively bronchiectasis may occur following severe episodes of pneumocystis pneumonia and may have contributed to this man's respiratory illness. The finding of confluent shadowing in the upper zones of both lungs on the chest radiograph suggested a clinical diagnosis of pneumocystis pneumonia particularly as he had been receiving inhaled pentamidine as secondary prophylaxis. Some patients receiving this form of prophylaxis may relapse and present with upper lobe pneumocystis pneumonia.

Discussion (Dr Noeleen Foley)

This patient's history illustrates one of the most common clinical problems in AIDS, namely diarrhoea, and one of its least frequent causes: *Clostridium difficile*. Dr Williams has discussed the differential diagnosis of diarrhoea in patients with advanced disease and I agree that CMV infection would be high on the list, as either a co-pathogen or sole agent, particularly during the second episode described, when there was little diarrhoea but rectal bleeding occurred and the plain abdominal radiograph showed thumb-printing.

Diarrhoea is one of the most frequent symptoms in patients with AIDS, occurring in up to 90% of patients.[10] There is also some evidence that patients with AIDS who have diarrhoea have a greater degree of immune suppression than those who do not have this symptom. In the majority of patients, an infectious pathogen can be identified in the stool (up to 80%) and diarrhoea may be polymicrobial.[1 2 7 10] The organisms responsible vary depending on the geographical area in which the patient lives and the stage of disease. Among the commonest pathogens in European and North American patients are bacteria such as *Salmonella*, *Shigella* and *Campylobacter*, mycobacteria such as *M avium intracellulare*, parasites such as *Entamoeba histolytica* and viruses such as adenovirus and cytomegalovirus.

In a review of diarrhoea in patients with AIDS a three stage protocol for investigation has been suggested.[2] (table 2) In practice most units would carry out the investigations described in step 1 in all patients, although examination for *C difficile* toxin is not routine

Table 2 Investigation of diarrhoea in patients with AIDS

Step 1
(a) Culture stool for *Salmonella* species, *Shigella flexneri* and *Campylobacter jejuni* (minimum 3 samples).
(b) Assay for *Clostridium difficile* toxin.
(c) Stain and culture stool for alcohol and acid fast bacilli (AAFB) and fungi.
(d) Examine stool for parasites.

Step 2
(a) Sigmoidoscopy and rectal biopsy.
(b) Endoscopy (colonoscopy and oesophagogastroduodenoscopy) in order to examine bowel and obtain biopsy specimens and luminal material.
(c) Colonic biopsy specimens cultured for CMV, adenovirus, mycobacteria and *Herpes simplex* virus.
(d) Duodenal biopsy specimens cultured for CMV and mycobacteria.
(e) Staining of biopsy specimens for protozoa, viral inclusions and AAFB.
(f) Staining of duodenal fluid for protozoa.

Step 3
Electron microscopy examination of biopsy specimens for *Microsporidia* (duodenal biopsy) and adenovirus (colonic biopsy).

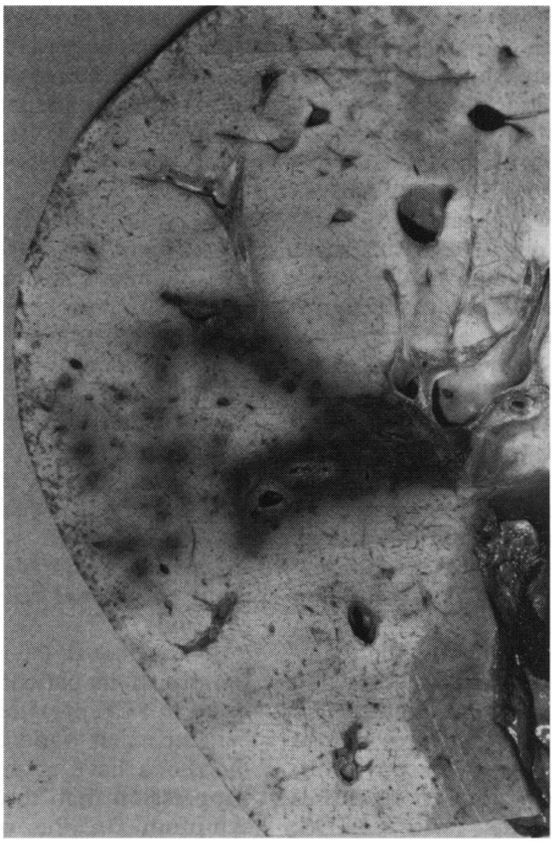

Figure 4 Liver showing dark red lesions of Kaposi's sarcoma extending from the portal tracts.

in many centres. Sigmoidoscopy and biopsy are commonly performed but the results of these investigations are usually awaited before proceeding to colonoscopy or upper gastrointestinal endoscopy.

It is important to note that there is a high yield of specific pathogens in patients with AIDS, that infection with enteric pathogens rarely resolves spontaneously and that specific therapy brings about improvement in up to 75% of cases. In this case, specific therapy appears to have been effective, but the symptoms relapsed more frequently than is usual with *C difficile*. Organisms of *C difficile* may persist after treatment which has effectively eliminated the toxin and there is a recurrence rate of up to 20%.

Clinical diagnoses: 1. Pseudomembranous colitis due to *Clostridium difficile*.
2. Cutaneous, palatal and endobronchial Kaposi's sarcoma.
3. Recurrent, apical pneumocystis pneumonia?

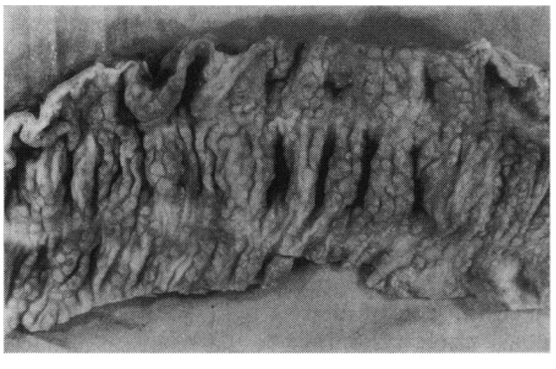

Figure 5 Transverse colon showing multiple small plaques of exudate, typical of pseudomembranous colitis (unstained).

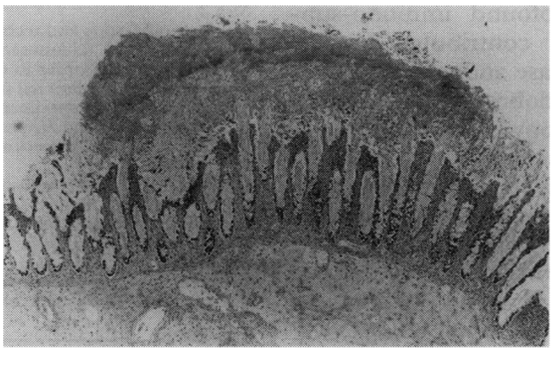

Figure 6 Colon histology: showing typical lesions of pseudomembranous colitis with a plaque of exudate over dilated degenerate crypts (haematoxylin and eosin, magnification × 20).

Pathology (Dr S B Lucas)

The body was that of a thin black man. On the trunk and limbs were many lesions of Kaposi's sarcoma. The main pathological abnormalities were found in the respiratory and alimentary tracts.

In the lungs there were Kaposi's sarcoma in the trachea and in the lower lobe bronchi and lower zone parenchyma. Also Kaposi's was present in the hilar lymph nodes. In the upper zones there was extensive *Pneumocystis carinii* pneumonia with calcification—reflecting chronicity. Small lesions of Kaposi's were also found on the palate, on the oesophagus, jejunum and in the caecum. Lesions were also found in the liver radiating out from the portal tracts. (fig 4)

In the large bowel there was severe pseudomembranous colitis extending from the caecum to rectum (figs 5 & 6) but there was no histological evidence of CMV. In the left testis there was scarring, and Gram-negative rods seen in vessel walls were indicative of *Pseudomonas* infection.

The brain had only very scanty non-specific microglial nodules. Multiple sections of the right eye failed to reveal CMV infection.

Pathological diagnoses: 1. Pseudomembranous colitis.
2. *Pneumocystis carinii* pneumonia of upper lobes.
3. Kaposi's sarcoma of skin, lungs, bowel.
4. Residual Gram-negative rod infection.

Discussion (Dr R F Miller)

Since this case we have seen two other HIV positive patients with *Clostridium difficile* diarrhoea. The first was a 45 year old heterosexual Caucasian man who became neutropenic secondary to chemotherapy given for treatment of disseminated non-Hodgkin's lymphoma. He had received intravenous ceftazidime as empirical treatment for neutropenic fever and then developed diarrhoea. *Clostridium difficile* was identified in the stool; his symptoms resolved with oral vancomycin therapy. The second patient, a 42 year old homosexual Caucasian man, developed *Clostridium difficile* diarrhoea whilst receiving

rifampicin, ethambutol and clarithromycin as treatment for disseminated *Mycobacterium avium-intracellulare* infection and co-trimoxazole as secondary prophylaxis against pneumocystis pneumonia.

We thank Jane Healing for typing the manuscript.

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